REMARKS

Claims 1-33 are pending in this application. Claims 21-33 have been withdrawn from consideration by the Examiner as being directed toward a non-elected invention. Claims 21-33 are canceled herein without prejudice or disclaimer. Claims 1-11, 13-14 and 20 are amended herein for clarity to more particularly define the invention. New claims 34-38 are added herein. Support for these amendments and new claims is found in the language of the original claims and throughout the specification, as set forth below. It is believed that no new matter is added by these amendments and new claims and their entry and consideration are respectfully requested. In light of these amendments, the new claims and the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

I. Objection to claim 1

The Office Action states that claim 1 is objected to for the recitation of the word "fist," which should be the word "first." Claim 1 as presented herein properly recites first rather than fist, thereby mooting this objection and applicants respectfully request its withdrawal.

II. Rejections under 35 U.S.C. § 112, second paragraph

The Office Action states that claims 1-20 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Reconsideration is respectfully requested in view of the remarks below.

A. The Office Action states that claims 1-20 are allegedly indefinite in the recitation of "an anchor" in claim 1 because the definition in the specification at page 8 is ambiguous. Applicants submit that one of ordinary skill in the art would readily understand the definition of "an anchor" as claimed herein when read in light of the specification. As noted in the Office Action, the specification states that "the anchor can be any compound which is capable of binding to a second segment of the target RNA sequence. The anchor preferably is an, optionally modified, oligonucleotide or a protein." Specification at page 8, lines 12-15.

Furthermore, the definition of an anchor would be apparent to one of ordinary skill in the

art based on the function of the anchor. As stated in the specification, "[d]ue to the presence of the anchor, the primer is able to bind specifically to the target RNA sequence. The hybridizing sequence alone would not be able to bind specifically, due to its short length." Specification at page 8, lines 8-11. See also, specification at page 4, lines 11-18. Thus, because the anchor assists the primer in binding to the target sequence, one of ordinary skill in the art would understand that the anchor must be a compound that is capable of binding to a segment of the target sequence, such as an oligonucleotide or protein, so as to expose and enable the hybridizing sequence to bind to the target sequence. Thus, applicants submit that the term "anchor" is clarified. However, to expedite prosecution of this application, the claims as presented herein recite an oligonucleotide anchor and applicants reserve the option of pursuing claims reciting "an anchor" consistent with the scope of this term as defined in the specification in further continuation applications.

The Examiner also states that the specification allegedly does not provide a limiting definition as to what is encompassed by the recitation of an "optionally modified oligonucleotide." Applicants submit that the phrase optionally modified oligonucleotide would be understood by one of ordinary skill in the art when read in light of the specification. A description of exemplary modified nucleotides is given in the specification on page 8, lines 30-33 and page 9, lines 1-2. However, in order to expedite prosecution of this application, the claims as presented herein do not recite an optionally modified oligonucleotide, thereby mooting this rejection.

B. The Office Action states that claims 1-20 are allegedly indefinite for the recitation of "amplification enhancing sequences" in claim 1. The Office Action further states that "the definition is confusing because it cannot be determined if the recitation of 'an amplification sequence' suggests that the primer has a random region that is semi-circled or loop or if the term is intended to mean a nonspecific region with no promoter or something completely different." Office Action, page 3. The Office Action additionally states that it cannot be determined how these random, non-specific sequences result in "enhancing" amplification of RNA.

Applicants submit that one of ordinary skill in the art would understand the definition of "amplification enhancing sequence" when read in light of the specification. As pointed out in

the Office Action, the specification states that "an amplification enhancing sequence is a non-specific nucleic acid vis-à-vis the target sequence, but it comprises no promoter, i.e. only a random sequence that generates a loop between the anchor and the hybridizing sequence." Specification at page 12, lines 32-33 and page 13, lines 1-2. One of ordinary skill in the art would understand that the amplification enhancing sequence as recited in claim 1 is a non-specific nucleic acid with regard to the target sequence. Thus, it is a random nucleic acid sequence, which comprises no promoter and generates a loop between the anchor and the hybridizing sequence upon annealing of the second primer to the first single stranded cDNA sequence.

Applicants further point out that the amplification enhancing sequence enhances amplification by creating a loop between the oligonucleotide anchor and the hybridizing sequence of 7 to 14 nucleotides of the second primer when each binds to a first and second segment, respectively, of the first single stranded cDNA sequence, facilitating amplification thereof. Accordingly, applicants submit that the phrase "amplification enhancing sequence" is clarified.

C. The Office Action states that claims 1-20 are indefinite for the recitation of "capable of" in claim 1. Claim 1 is amended herein as suggested by the Examiner to recite an anchor that binds, rather than an anchor that is capable of binding. Support for this amendment is found throughout the specification at least, for example, on page 4, lines 19-27.

D. The Office Action states that claim 1 lacks proper antecedent basis in step (f) for the recitation of "the promoter sequence comprised in the first primer." Claim 1 as presented herein in step (a) recites that said first primer comprises a first hybridizing sequence and a promoter sequence, wherein the promoter sequence is operatively associated with the first hybridizing sequence and the first hybridizing sequence is complementary to and hybridizes to at least a first segment of the target RNA sequence. Support for this amendment is found in the language of the original claim and throughout the specification at least, for example, on page 6, lines 22-27. Thus, claim 1 has proper antecedent basis for the recitation of a promoter sequence in the first primer.

E. The Office Action states that claim 13 is indefinite for the recitation of "wherein the transcription enhancing sequence reads ... SEQ ID NO: 39." Claim 13 as presented herein recites that the transcription enhancing sequence comprises the nucleotide sequence of SEQ ID NO:39, thereby rendering this claim definite.

F. The Office Action further states that claim 14 is indefinite for the recitation of "wherein the amplification enhancing sequence reads ... SEQ ID NO: 40." Claim 14 as presented herein recites that the transcription enhancing sequence comprises the nucleotide sequence of SEQ ID NO:40, thereby rendering this claim definite.

Having addressed the Examiner's concerns raised in the Office Action with respect to indefiniteness, applicants respectfully request that all rejections of claims 1-20 under 35 U.S.C. § 112, second paragraph, be withdrawn.

III. Rejection under 35 U.S.C. § 103

The Office Action states that claims 1-12 and 15-20 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Dahl et al. (US 2004/0197802). Specifically, the Office Action states that, regarding claims 1-7 and 12, Dahl et al. teaches a method for amplification of a target RNA, "wherein the method may comprise anchor sequences associated with the primer, DNA polymerization or reverse transcriptase enhancers and hybridizing portions of the primer that hybridizes to segments of the target nucleic acid (RNA) associated with the promoter." Office Action page 6. The Examiner acknowledges that Dahl et al. does not teach the different length limitations of components of the primers but that Dahl et al. allegedly teaches that the primers have an average of 18 to 22 nucleotides in length. The Examiner then cites *In re Aller* in support of the contention that the selection of the length of the different primer components would be routine optimization. It is therefore the Examiner's position that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of this invention to perform the RNA amplification reaction as taught by Dahl et al. under the same reaction conditions.

Applicants respectfully traverse this rejection on the basis that the claimed invention would not have been obvious to one of ordinary skill in the art at the time this invention was

made and that the Examiner has failed to meet all of the requirements for a *prima facie* showing of obviousness. As stated in the Examination Guidelines for Determining Obviousness, "the Supreme Court reaffirmed the familiar framework for determining obviousness as set forth in *Graham v. John Deere Co*...." ("Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*" Federal Register Vol. 72, No. 195, 57526-57535, 57526). Hence, and as long established under that framework, to establish a *prima facie* case of obviousness, three requirements must be satisfied (M.P.E.P. § 2143). First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some **suggestion or incentive that would have motivated** the skilled artisan to modify a reference or to combine references. *In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the proposed modification or combination of the prior art must have a **reasonable expectation of success**, determined from the vantage point of the skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Third, the prior art reference or combination of references **must teach or suggest all of the limitations of the claims**. *See In re Wilson* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art"). In the present rejection, the cited reference fails to teach or suggest all of the limitations of the claims. Thus, the Examiner has failed to make a *prima facie* case of obviousness.

Specifically, claim 1 as presented herein recites a method for amplification of a target RNA sequence comprising the following steps: (a) annealing a first primer to the target RNA sequence, said first primer comprising a first hybridizing sequence and a promoter sequence, wherein the promoter sequence is operatively associated with the first hybridizing sequence and the first hybridizing sequence is complementary to and hybridizes to at least a first segment of the target RNA sequence; (b) extending said first primer in a reaction catalyzed by a DNA polymerase, forming a first RNA/cDNA hybrid nucleic acid molecule; (c) selectively removing the target RNA sequence of the first RNA/cDNA hybrid nucleic acid molecule forming a first single stranded cDNA sequence; (d) annealing a second primer to the obtained first single

stranded cDNA sequence, said second primer comprising a second hybridizing sequence which is complementary to and hybridizes to a first segment of the first single stranded cDNA sequence; (e) extending said second primer in a reaction catalyzed by a DNA polymerase to form a first double stranded DNA molecule; and (f) employing the first double stranded DNA molecule of step (e) in the preparation of a plurality of RNA transcripts that are complementary to the target RNA sequence in a reaction catalyzed by a DNA-dependent RNA polymerase with specificity for the promoter sequence comprised in said first primer, wherein said first primer comprises a first hybridizing sequence of 7 to 14 nucleotides, a transcription enhancing sequence comprising said promoter sequence, and a first oligonucleotide anchor that binds to a second segment of the target RNA sequence, whereby the transcription enhancing sequence creates a loop between the first oligonucleotide anchor and the first hybridizing sequence upon annealing of said first primer to the target RNA sequence and/or wherein said second primer comprises a second hybridizing sequence of 7 to 14 nucleotides, an amplification enhancing sequence comprising no promoter sequence and a second oligonucleotide anchor that binds to a second segment of the first single stranded cDNA, whereby the amplification enhancing sequence creates a loop between the second oligonucleotide anchor and the second hybridizing sequence upon annealing of said second primer to the first single stranded cDNA sequence.

Support for the recitation in claim 1 of a first primer comprising "a first hybridizing sequence of 7 to 14 nucleotides, a transcription enhancing sequence comprising said promoter sequence, and a first oligonucleotide anchor that binds to a second segment of the target RNA sequence, whereby the transcription enhancing sequence creates a loop between the first oligonucleotide anchor and the first hybridizing sequence upon annealing of said first primer to the target RNA sequence" is found throughout the specification and at least, for example, on page 12, lines 26-31.

Furthermore, support for the recitation of a second primer comprising "a second hybridizing sequence of 7 to 14 nucleotides, an amplification enhancing sequence comprising no promoter sequence and a second oligonucleotide anchor that binds to a second segment of the first single stranded cDNA, whereby the amplification enhancing sequence creates a loop between the second oligonucleotide anchor and the second hybridizing sequence upon annealing

of said second primer to the first single stranded cDNA sequence" is found throughout the specification and at least, for example, on page 12, lines 32-33 and page 13, lines 1-2.

Thus, the present invention provides methods for amplification of a target RNA sequence that employ a first primer having the above-recited claimed elements and/or a second primer having the above-recited claimed elements. Dahl et al. does not teach or suggest either the first primer of this invention, the second primer of this invention or their combination in any methods of amplification. In particular, to the extent that Dahl et al. describes what is referred to as an "anchored" primer, such description is set forth in paragraph 189 of Dahl et al. as follows.

> An "anchored oligo d(T) promoter primer," in addition to having an oligo(dT) sequence in its 3'-portion, also has one (or a small number) of nucleotides 3'-of the oligo(dT) sequence, called "anchor nucleotides," which anneal to the 3'-portion of the mRNA target sequence just prior to the poly(A) sequence. Thus, the anchor nucleotides serve to "anchor" the mRNA-complementary portion of the anchored oligo(dT) promoter primer to the beginning of the protein-coding sequence of the mRNA target sequence.

This anchored oligo d(T) promoter primer of Dahl et al. would be readily recognized by one of ordinary skill in the art to be clearly distinguished from the oligonucleotide anchor of the present invention. Furthermore, Dahl et al. fails to teach or suggest the use of a transcription enhancing sequence comprising a promoter in a first primer and/or the use of an amplification enhancing sequence comprising no promoter in a second primer in order to create a loop between the anchor and a hybridizing sequence of only 7 to 14 nucleotides upon annealing of the first and/or second primers to their respective target sequences. Thus, Dahl et al. fails to teach or suggest all the limitations of the invention as claimed herein, as required under 35 U.S.C. § 103(a). Therefore, the Examiner has failed to make a *prima facie* showing of obviousness of this invention and accordingly, applicants respectfully request that this rejection be withdrawn.

IV. New claims 34-38

New claim 34 recites the method of claim 8, wherein the modified nucleotides of the first oligonucleotide anchor comprise 2'O-methyl modified nucleotides and/or LNA. Support for this new claim is found in the language of original claim 8 and in the specification, at least for

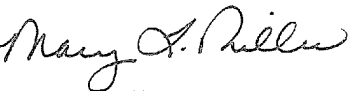
example, on page 8, lines 30-33. New claim 35 depends from claim 11 and recites that the second oligonucleotide anchor comprises DNA, RNA or modified nucleotides. New claim 36 depends from claim 35 and further recites that the modified nucleotides of the second oligonucleotide anchor comprise 2'O-methyl modified nucleotides and/or LNA. Support for these new claims is found in the language of original claim 8. New claim 37 depends from claim 1 and recites that the second oligonucleotide anchor comprises PNA. Support for this claim is found in the language of original claim 9. Finally, new claim 38 depends from claim 1 and recites that the second hybridizing sequence of said second primer comprises 7-10 nucleotides which are complementary to a first segment of the first single stranded cDNA sequence of 7 to 10 contiguous nucleotides. Support for this claim is found in the language of original claim 5 and in the specification, at least for example, on page 8, lines 3-7.

New claims 34-38 are believed to be free of all of the rejections cited above for pending claims 1-20 for all of the reasons articulated herein in support of these pending claims. Thus, entry and allowance of these new claims are respectfully requested.

Having addressed all of the issues raised in the present Office Action, applicants believe the present application to be in condition for allowance, which action is respectfully requested. The Examiner is encouraged to contact the undersigned directly, if such contact will expedite the examination of the pending claims and their allowance to issue.

The Commissioner is authorized to charge Deposit Account No. 50-0220 in the amount of $130.00 as the fee for a one month extension of time. This amount is believed to be correct. However, the Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account no. 50-0200

Respectfully submitted,



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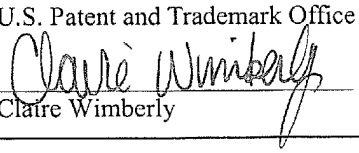

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